Letters to the Editor

Auditory Hallucinations Associated With Topiramate

Sir: The traditional antiepileptic drugs, such as carbamazepine and valproic acid, may precipitate psychosis in patients being treated for seizures. The efficacy of these agents in the management of bipolar disorder is well established. Recently, a new class of antiepileptic drugs has been used for the treatment of both seizures and bipolar disorder. However, there have been reports of psychosis among epileptics caused by the newer antiepileptic drugs, including topiramate.[1] We describe a case of psychosis associated with topiramate in a patient with no history of seizures.

Case report. Ms. A, a 28-year-old white woman, had a history of schizoaffective disorder, bipolar type (DSM-IV criteria). She had experienced several manic periods, as well as episodes of psychosis in the past, characterized by delusions and auditory hallucinations. Specifically, during prior psychotic episodes she described "hippos running through my head" and "lots of voices . . . I don't know who they were." She had been treated with quetiapine, up to 500 mg q.h.s., and had been free of positive psychotic symptoms for several months. Ms. A also had a history of migraine headaches without aura. A computed tomographic scan of the head had shown no abnormalities, and she had experienced moderate reduction in the frequency and severity of headaches from conservative management with nonsteroidal anti-inflammatory drugs. She had been unable to tolerate several prophylactic medications, such as valproic acid, due to weight gain. Although she had never had an electroencephalogram (EEG), extensive chart review and patient and family interviews revealed no evidence of seizures at any time. Also, Ms. A had a history of anorexia nervosa and in her late teen years had a body weight as low as 89 lb (40 kg). Although she had been within 10 lb (4.5 kg) of her ideal body weight for the previous 2 years, she was quite skeptical of any medication that may cause weight gain.

With this history in mind, a trial of topiramate was initiated as a prophylactic agent for headaches. After 2 days of taking topiramate, 25 mg b.i.d., Ms. A visited her psychiatrist and described "lying on the beach last night and hearing voices from the center of the earth coming up through the sand." She also described "hearing Charles Manson saying bad things to me." Topiramate was discontinued, and, after 2 days, Ms. A returned to her baseline mental status. Psychotic symptoms were no longer present. Although urine toxicology was not performed, Ms. A and her husband, both of whom had been quite reliable, denied use of illicit drugs.

The association between psychosis and epilepsy has been recognized for decades. Landolt described how suppression of seizures with ethosuximide led to a normalization of a previously abnormal EEG and to the development of psychosis, a phenomenon he called "forced normalization."[2] The term *alternative psychosis* has been used to describe the development of psychosis with antiepileptic drugs but without concomitant EEG changes.[2] To our knowledge, this is the first report of psychosis associated with topiramate in a patient without a history of seizures. Although the particular psychotic symptoms this patient experienced were unusual, they were not experienced at any time in the past and were presumably new phenomena. While its mechanism of action is not fully understood, topiramate acts on voltage-gated Na^+ channels, γ-aminobutyric acid (GABA)-A receptors, and glutamate receptors. Low GABA function may be an inherited biological marker of vulnerability to mood disorders,[3] and plasma GABA levels may predict response to antimanic agents.[4] Also, cerebrospinal fluid glutamate concentration has been shown to inversely correlate with degree of positive psychotic symptoms.[5] Topiramate has great utility in the management of psychiatric illness and epilepsy. However, clinicians should be aware that topiramate may be associated with the development of psychotic symptoms, even in patients without a history of seizures, through a poorly understood mechanism that involves multiple neurotransmitter systems and through the suppression of seizure activity via forced normalization.

References

1. Khan A, Faught E, Gilliam F, et al. Acute psychotic symptoms induced by topiramate. Seizure 1999;8:235–237
2. Tellenbach H. Epilepsy as a seizure disorder and as a psychosis: on alternative psychosis of a paranoid type with "forced normalization" (Landolt) of the encephalogram of epileptics. In: Trimble MR, Schmitz B, eds. Forced Normalization and Alternative Psychoses of Epilepsy. Petersfield: Wrightson Biomedical Publishing; 1998:49–66
3. Petty F. GABA and mood disorders: a brief review and hypothesis. J Affect Disord 1995;34:275–281
4. Petty F, Rush AJ, Davis JM, et al. Plasma GABA predicts acute response to divalproex in mania. Biol Psychiatry 1996;39:278–284
5. Faustman WO, Bardgett M, Faull KF, et al. Cerebrospinal fluid glutamate inversely correlates with positive symptom severity in unmedicated male schizophrenic/schizoaffective patients. Biol Psychiatry 1999;45:68–75

Scott C. Matthews, M.D.
Brian P. Miller, M.D.
University of California, San Diego
La Jolla, California

Metformin in Obesity Associated With Antipsychotic Drug Administration: A Pilot Study

Sir: Excessive body weight gain is now recognized as an important side effect of chronic administration of typical and atypical antipsychotic drugs.[1,2] The prevention and treatment of antipsychotic-induced body weight gain are particularly difficult, and new strategies are needed.[3]

Table 1. Sex, Body Mass Index (BMI), and Pharmacologic Treatment

Patient	Age, y	BMI,[a] (kg/m^2)	Antipsychotic Treatment, dosage (y)[b]	Metformin Daily Dose, mg
1	49	36.7	Haloperidol depot, 50 mg every 3 weeks (15)	1000–1700
2	34	28.8	Trifluoperazine, 10 mg/d (3)	1000–1700
3	45	36.3	Fluphenazine depot, 25 mg every 3 weeks (7)	500–2550
4	32	43.8	Risperidone, 9 mg/d (18)	500–2125
5	36	29.6	Risperidone, 9 mg/d (15)	500–2550

[a]Before starting placebo.
[b]Number of years receiving treatment with any antipsychotic medication.

Convergent evidence suggests that antipsychotic administration modifies glucose metabolism and serum insulin levels.[2,4–6] Collectively, the data point to an antipsychotic-induced impairment in insulin sensitivity, which may be involved in body weight gain.[2] The oral antidiabetic agent metformin improves insulin sensitivity and decreases body weight in subjects with diabetes, polycystic ovary syndrome, and primary obesity.[7–9] We conducted a pilot study in obese psychiatric patients who received metformin (Merck, Venezuela) in a double-blind, placebo-controlled protocol. We predicted a significant metformin-induced decrease in body weight and in the areas under the glucose and insulin curve. The area under the curve calculation proportionally integrates the values of glucose or insulin in fasting conditions and after a glucose overload (glucose tolerance test).

Method. Five women with chronic schizophrenia (DSM-IV) daily attending the outpatient clinic at San Juan de Dios Hospital (Mèrida, Venezuela) entered the study, having given written informed consent. Subjects had been treated with antipsychotics for many years, and they wanted to lose body weight. The patients were informed that the treatment might induce body weight loss, but no attempt was made to place them on a diet or specific physical exercise program. The study lasted 12 weeks. In a blind condition, placebo was administered during the first 4 weeks and metformin (500–2550 mg/day) during the last 8 weeks. Treatments were administered 3 times a day by the nursing staff. Metformin side effect control and dosage adjustment were conducted daily by a psychiatrist (L.A.P.). An oral glucose tolerance test (75 g of glucose at 7:00 a.m.) was performed on the first and last days of placebo treatment and on the last day of metformin treatment. Hence, the test on the last day of placebo treatment provides baseline values for the metformin trial. Patients were weighed weekly, and the Brief Psychiatric Rating Scale (BPRS)[10] was administered weekly by a physician who was blind to the treatment schedule (E.C.B).

Serum prolactin, insulin, and glucose levels were measured with commercial kits (Diagnostic Products Corporation, Los Angeles, Calif.) in a single assay (the intra-assay variation was below 10%). Data (expressed as mean ± SEM) were analyzed by the Wilcoxon signed rank test for paired samples. Results were considered significant when $p \leq .05$.

Results. Table 1 lists the age, body mass index, antipsychotic type and dosage, and metformin dose for each patient. Placebo pills were well tolerated, but metformin induced mild gastrointestinal discomfort, which necessitated frequent dose adjustment at the beginning of the treatment period.

Table 2. Body Weight, Brief Psychiatric Rating Scale (BPRS) Score, and Glucose and Insulin Area Under the Curve (AUC) Values After Placebo and Metformin Treatment

	Placebo		Metformin	
Outcome Variable	Week 0	Week 4	Week 8	Week 12
Body weight, kg				
1	96.2	89.5	88.1	88.5
2	70.2	71.1	70.0	68.4
3	79.6	71.6	71.5	71.0
4	110.4	108.4	108.2	105.5
5	78.5	77.5	78.4	78.0
Total sample[e]	86.9 ± 7.2	83.6 ± 7.1[a]	83.2 ± 7	82.3 ± 6.7
BPRS score				
1	21	14	15	14
2	15	7	5	8
3	12	6	6	3
4	12	5	10	15
5	23	12	14	14
Total sample[e]	16.6 ± 2.2	8.8 ± 1.7[b]	10.0 ± 2.1	10.8 ± 5.1
Glucose AUC, mg/dL				
1	302.3	299.5	...	370.3
2	211.8	169.0	...	251.8
3	274.3	298.3	...	347.0
4	249.0	226.8	...	340.0
5	235.1	246.3	...	316.0
Total sample[e]	254.4 ± 15.6	247.9 ± 24.0	...	325.0 ± 20.0[c]
Insulin AUC, mIU/mL				
1	124.9	70.2	...	118.1
2	114.1	180.1	...	343.9
3	229.3	182.3	...	241.9
4	200.9	92.8	...	111.1
5	226.4	171.5	...	200.3
Total sample[e]	179.1 ± 24.0	141.1 ± 22.0	...	203.1 ± 43.0[d]
Serum glucose, mg/dL[e]	134.2 ± 10.5	114.8 ± 13.7	...	115.0 ± 7.9
Serum insulin, mIU/mL[e]	17.2 ± 1.9	12.5 ± 0.8	...	15.4 ± 2.3

[a]$z = 1.75$, $p = .08$ vs. week 0 (before start of placebo).
[b]$z = 2.1$, $p = .039$ vs. week 0 (before start of placebo).
[c]$z = 2.02$, $p = .043$ vs. week 4 (baseline for metformin).
[d]$z = 2.2$, $p = .037$ vs. week 4 (baseline for metformin).
[e]Mean ± SEM.

The mean serum prolactin level was 38.4 ± 17.0 ng/mL. During placebo administration, the patients lost 3.3 ± 1.7 kg (7.3 ± 3.8 lb; $p = .08$), whereas during metformin treatment they lost 1.3 ± 1.1 kg (2.9 ± 2.4 lb; not significant). During placebo, patients 1 and 3 lost 6.7 and 8 kg (14.9 and 17.8 lb), respectively, whereas the weight change in the other subjects averaged 0.6 kg (1.3 lb). The glucose and insulin areas under the curve did not change significantly during placebo treatment, but they significantly increased during metformin administration ($p = .043$ and $p = .037$, respectively). The BPRS scores significantly decreased during placebo ($p = .039$) but did not change during metformin administration (Table 2).

Discussion. Contrary to our expectations, the body weight loss was higher during placebo than during metformin administration, and the areas under the curve for glucose and insulin increased during the drug treatment. The body weight loss during placebo treatment may be related to the strong motivation the patients had at the start of the treatments, which may have led them to decrease food intake and increase exercising. Since metformin was added when some subjects had lost a considerable amount of weight, it may have prevented additional body weight loss. However, metformin displayed a modest effect on

body weight even in those patients with little change during placebo treatment (subjects 2, 4, and 5).

This study has several drawbacks: a small sample, no randomized design, and a relatively short period of metformin administration. However, in studies conducted in nonpsychiatric populations, even without diet control, a significant body weight loss occurred in the first months of treatment.[7–9] We have no explanation for the increase in the areas under the curve for glucose and insulin after treatment with metformin was initiated, and no patient was previously known to be clinically diabetic. It is an open question whether the antipsychotic-induced insulin resistance is similar to that observed in primary obesity.[2] The insulin resistance may be related to hyperprolactinemia,[11–13] but other explanations must be provided for antipsychotics that do not increase prolactin as much, such as clozapine, quetiapine, and olanzapine.[2] It is tempting to speculate that different patterns of insulin resistance may be observed during treatment with typical and atypical antipsychotics, and in diabetes and primary obesity (in which hyperprolactinemia is unusual). Hence, an anomalous insulin response to metformin might be observed, and metformin-responsive subjects may be identified.

In any event, given the lack of significant physical or mental side effects during metformin administration, the replication and expansion of this study in a crossover, placebo-controlled design with a higher number of patients may be worthwhile. Our results also reinforce the importance of placebo control groups in clinical trials for weight loss among patients with schizophrenia.

This study was supported by the Consejo de Desarrollo Cientifico, Humanístico y Tecnológico, Universidad de Los Andes, Venezuela.

References

1. Allison DB, Mentore JL, Heo M, et al. Antipsychotic-induced weight gain: a comprehensive research synthesis. Am J Psychiatry 1999;156:1686–1696
2. Baptista T. Body weight gain induced by antipsychotic drugs: mechanisms and management. Acta Psychiatr Scand 1999;100:3–16
3. Green AI, Patel JK, Goisman RM, et al. Weight gain from novel antipsychotic drugs: need for action. Gen Hosp Psychiatry 2000;22: 224–235
4. Yazici KM, Erbas T, Yazici AH. The effect of clozapine on glucose metabolism. Exp Clin Endocrinol Diabetes 1998;106:475–477
5. Melkersson KI, Hulting A-L, Brismar KE. Different influences of classical antipsychotics and clozapine on glucose-insulin homeostasis in patients with schizophrenia or related psychoses. J Clin Psychiatry 1999;60:783–791
6. Baptista T, Lacruz A, Silvera R, et al. Endocrine and metabolic profile of women after chronic administration of typical antipsychotic drugs: relationship with body weight regulation. In: 30th Annual Meeting, Society for Neuroscience; November 2000; New Orleans, La. Abstract 502.11
7. Bailey CJ. Insulin resistance and antidiabetic drugs. Biochem Pharmacol 1999;58:1511–1520
8. Velasquez E, Mendoza S, Harner T, et al. Metformin therapy in polycystic ovary syndrome reduces hyperinsulinemia, insulin resistance, hyperandrogenemia, and systolic blood pressure, while facilitating normal menses and pregnancy. Metabolism 1994;5: 647–654
9. Fontbonne A, Charles MA, Juhan Vague I, et al, for the BIGPRO Study Group. The effects of metformin on the metabolic abnormalities associated with upper-body fat distribution. Diabetes Care 1996; 19:920–926
10. Overall JE, Gorham DR. The Brief Psychiatric Rating Scale. Psychol Rep 1962;10:799–812
11. Schernthaner G, Prager R, Punzengruber C, et al. Severe hyperprolactinemia is associated with decreased insulin binding in vitro and insulin resistance in vivo. Diabetologia 1985;28:138–142
12. Cabrera R, Mayor P, Fernàndez-Ruiz J, et al. Insulin binding and action on adipocytes from female rats with experimentally induced chronic hyperprolactinemia. Mol Cell Endocrinol 1988;58:167–173
13. Foss MC, Paula FJ, Paccola GM, et al. Peripheral glucose metabolism in human hyperprolactinemia. Clin Endocrinol 1995;43:721–726

Trino Baptista, M.D.
Luis Hernàndez, M.D.
Los Andes University Medical School
Lisette Alvarez Prieto, M.D.
Evelyn Cubillàn Boyero, M.D.
San Juan de Dios Hospital
Soaira de Mendoza, M.D.
Metabolism Center
Mèrida, Venezuela

Reboxetine-Induced Hypomania

Sir: Hypomanic episodes are part of the core symptoms of bipolar I and II disorders, appearing either spontaneously or during the treatment of bipolar depression with antidepressant drugs. The potential to induce manic and hypomanic episodes by different types of antidepressants is currently a controversial issue. However, tricyclic antidepressants are generally considered more dangerous in the treatment of bipolar depression in regard to the phenomenon of induction of hypomania or mania and cycle acceleration.[1] Serotonin reuptake inhibitors are considered safer,[2] even though the pathophysiology of the switch process is still unknown and may involve several neurotransmitter systems.[3]

Reboxetine has recently been marketed in Europe as an antidepressant drug with a selective action in the reuptake of norepinephrine.[4] Reboxetine has shown efficacy in the treatment of depression in several randomized clinical trials.[5] Its unique mechanism of action makes it very interesting theoretically in the treatment of several types of depression, such as bipolar depression.

To the best of our knowledge, there are no data on the capacity of reboxetine to induce manic or hypomanic episodes in depressed bipolar patients. During the clinical trials for reboxetine, which included only unipolar depressed patients (J. Massana, M.D., Ph.D., oral communication), 4 patients showed hypomanic or manic features that were reported as the side effect "manic reaction." We present case reports of the first 3 depressed bipolar patients that we treated with reboxetine, who showed a clear hypomanic switch shortly after the introduction of the drug.

Case 1. Mr. A, a 56-year-old man, had suffered approximately 9 manic episodes and even more depressive episodes throughout his life. At least 3 of his 9 manic episodes occurred within the first 4 weeks after starting treatment with tricyclic antidepressants. After a failed paroxetine trial for his last episode of depression (DSM-IV), he initiated treatment with reboxetine, 8 mg/day. Two weeks later, even though his treatment with lithium and valproate was maintained (serum levels were 0.8 mEq/L and 70 μg/mL, respectively), he started waking up much earlier, making unusual plans, and being talkative and irritable. After reboxetine was discontinued and 2 mg/day of clonazepam was added, his hypomanic symptoms abated and he fell progressively into his previous depressive state.

Case 2. Ms. B, a 26-year-old woman with DSM-IV bipolar disorder, had a history of rapid cycling and nonresponse to se-

lective serotonin reuptake inhibitors and imipramine. Even though her valproate levels were elevated to 87 μg/mL when reboxetine, 4 mg/day, was prescribed, 4 weeks later she presented with a sudden hypomanic episode that was clearly out of step with her previous history of rapid cycling.

Case 3. Mr. C, a 44-year-old man, had bipolar II disorder (DSM-IV) with several previous hypomanic and depressive episodes and a current severe psychotic depressive episode. He developed full-blown hypomania within 3 weeks after beginning treatment with lithium (his serum lithium level was 1 mEq/L), olanzapine, 5 mg/day, and reboxetine, 8 mg/day.

In both of the latter 2 cases, hypomanic symptoms improved after discontinuation of reboxetine and slight modifications of the dosages of the other drugs.

These 3 anecdotal cases give weight to the norepinephrine hypothesis of the switch process. Despite the observational nature of this report, 3 factors appear to support the causal relationship between reboxetine and hypomania: first, the consecutive nature of the cases—since these were the first 3 bipolar patients that we treated with this drug, it seems unlikely that the rapid cycling could be explained only by chance; second, the temporal relationship between the introduction of the drug and the emergence of hypomanic symptoms (2–4 weeks); finally, the improvement of hypomanic switches after the withdrawal of the drug, with only minor concomitant modifications of the other drugs.

Alternative explanations for these clinical observations are possible, and only controlled trials can give definitive information on the potential of antidepressant drugs to induce hypomania. However, we believe that this experience should give some caution to the use of reboxetine in the treatment of bipolar depression, even in patients treated with mood stabilizers. Drugs with action on norepinephrine receptors might be associated to higher risk of induction of mania or hypomania.

References

1. Altshuler LL, Post RM, Leverich GS, et al. Antidepressant-induced mania and cycle-acceleration: a controversy revisited. Am J Psychiatry 1995;152:1130–1138
2. Peet M. Induction of mania with selective serotonin reuptake inhibitors and tricyclic antidepressants. Br J Psychiatry 1994;164:549–550
3. Vieta E, Bernardo M. Antidepressant-induced mania in obsessive-compulsive disorder [letter]. Am J Psychiatry 1992;149:1282
4. Massana J. Reboxetine versus fluoxetine: an overview of efficacy and tolerability. J Clin Psychiatry 1998;59(suppl 14):8–10
5. Berzewski H, Van Moffaert M, Gagiano CA. Efficacy and tolerability of reboxetine compared with imipramine in a double-blind study in patients suffering from major depressive episodes. Eur Neuropsychopharmacol 1997;7(suppl 1):S37–S47

Eduard Vieta, M.D., Ph.D.
Francesc Colom, Ph.D.
Anabel Martínez-Arán, Ph.D.
María Reinares, Ph.D.
Antonio Benabarre, M.D.
Barbara Corbella, M.D.
Cristóbal Gastó, M.D., Ph.D.
Bipolar Disorders Program
Stanley Foundation Research Center
IDIBAPS
Hospital Clinic de Barcelona
University of Barcelona
Barcelona, Spain

Tiagabine Improves Panic and Agoraphobia in Panic Disorder Patients

Sir: Tiagabine prevents g-aminobutyric acid (GABA) uptake by inhibiting GABA transporter (GAT) 1, which is 1 of at least 4 distinct GABA transporters responsible for uptake of GABA into neurons and glial cells after synaptic release. Due to its inherent mechanism of action, tiagabine leads to a reduced neuronal excitability by increasing brain GABA levels, which in turn results in antiepileptic activity.[1,2] Apart from GABA's anticonvulsant effects, anxiolytic properties could also be assumed. Indeed, recent animal studies showed anxiolytic effects in the elevated plus-maze and the open field test in tiagabine-treated rats.[3] In a first step, to investigate putative anxiolytic properties of tiagabine in humans, 4 patients meeting DSM-IV criteria for panic disorder with or without agoraphobia were treated with tiagabine. Patients did not suffer from comorbid depression or other psychiatric disorders. Anxiety ratings were obtained using the Hamilton Rating Scale for Anxiety (HAM-A),[4] the Bandelow Panic and Agoraphobia Scale,[5] and a diary for daily notation of panic attacks. For a summary of findings, see Table 1.

Case 1. Ms. A, a 39-year-old nurse, had a history of panic attacks for more than 1 year. Three months before baseline evaluation, she developed severe agoraphobia in addition to panic attacks. Finally, she was no longer able to leave her apartment. At admission, she suffered from daily panic attacks with a feeling of dyspnea. She had received no prior treatment. She began treatment with 15 mg of tiagabine daily. After 4 weeks of treatment, she reported a reduction of panic attacks, anxiety, and, especially, agoraphobia. At a 3-month follow-up, Ms. A continued tiagabine intake and was without any relapse of panic attacks or agoraphobia.

Case 2. Mr. B, a 23-year-old office employee, reported panic symptoms with hyperventilation and fear of suffocation for 3 years. Moreover, he was suffering from agoraphobia and social avoidance. Mr. B had been treated with imipramine, 100 mg/day; mirtazapine, 30 mg/day; and cognitive-behavioral therapy for 6 months without satisfying effect. After starting treatment with tiagabine, 15 mg daily, he reported a moderate improvement of anxiety, a marked reduction of agoraphobia, and absence of panic attacks after 2 weeks. However, sedation and severe vertigo required discontinuation of tiagabine treatment. After switching to alprazolam and paroxetine, Mr. B's condition has remained stable.

Case 3. Ms. C, a 24-year-old woman, suffered from panic attacks with severe palpitations for 6 months. Moreover, she reported a severe agoraphobia with inability to be alone in public places. Prior treatment with imipramine, 75 mg daily for 5 weeks, and supportive psychotherapy was unsuccessful. Administration of tiagabine, 15 mg daily, led to a marked improvement of panic attacks and agoraphobia within 4 weeks of initiating treatment. At follow-up, she reported a total remission of symptoms after a further 4 weeks of tiagabine intake.

Case 4. Mr. D, a 59-year-old man, had a history of panic attacks for more than 10 years. He reported frequent panic attacks (with up to a maximum of 6 attacks per day) and severe anxiety feelings. He had previously had trials with numerous antidepressants and anxiolytics (dikaliumchlorazepate, 5 mg/day; mianserin, 60 mg/day; trazodone, 100 mg/day; opipramol, 100 mg/day; amitriptyline, 75 mg/day; and mirtazapine, 30 mg/day), with limited success over the last few years. After a 2-week period of treatment with tiagabine, 15 mg daily, Mr. D reported a marked improvement of panic and anxiety. After an additional

Table 1. Improvement of Panic and Agoraphobia During 4 Weeks of Tiagabine Treatment[a]

Patient	Baseline	Day 7	Day 14	Day 21	Day 28
Ms. A					
HAM-A score	28	33	18	23	20
Bandelow score	37	31	25	22	20
No. of attacks	2	1	0	0	0
Mr. B[b]					
HAM-A score	26	21	16		
Bandelow score	33	28	23	...	...
No. of attacks	2	0.5	0		
Ms. C					
HAM-A score	35	27	17	13	8
Bandelow score	34	21	23	24	16
No. of attacks	0.5	0.5	0.5	0	0
Mr. D					
HAM-A score	28	25	15	9	7
Bandelow score	28	17	10	2	2
No. of attacks	3	2	0.5	0	0

[a]Anxiety was rated using the Hamilton Rating Scale for Anxiety (HAM-A), the Bandelow Panic and Agoraphobia Scale, and a panic diary for monitoring the number of daily panic attacks. Numbers of attacks represent the mean number of daily panic attacks during the week preceding the respective rating day.
[b]Mr. B discontinued tiagabine treatment after 2 weeks.

4 weeks of tiagabine treatment, anxiety symptoms were almost remitted, and no more panic attacks had occurred. During the subsequent 5 months of tiagabine intake, Mr. D's condition remained stable, and he had no anxiety symptoms.

Our results suggest that administration of tiagabine may improve panic attacks and agoraphobia in patients with panic disorder and agoraphobia. The absence of dependency and withdrawal problems could be an advantage when compared with benzodiazepines, especially in patients with comorbid anxiety and substance abuse. Therefore, treatment with tiagabine might constitute a useful alternative to benzodiazepines. Moreover, sleep studies have shown that tiagabine and other agonists targeting the GABA binding site of the $GABA_A$ receptor produce a much more favorable sleep electroencephalographic profile than benzodiazepines, with no rapid eye movement (REM) suppression, an enhancement of slow-wave activity during non-REM sleep, and no withdrawal effects.[6,7] Our preliminary results suggest that treatment with the GABA reuptake inhibitor tiagabine could be an alternative treatment strategy for patients with panic disorder. Although this case series is encouraging concerning putative anxiolytic properties of tiagabine in humans, controlled studies and follow-up investigations are needed to delineate the therapeutic properties of tiagabine in anxiety disorders.

References

1. Adkins JC, Noble S. Tiagabine: a review of its pharmacodynamic and pharmacokinetic properties and therapeutic potential in the management of epilepsy. Drugs 1998;55:437–460
2. Schachter SC. A review of the antiepileptic drug tiagabine. Clin Neuropharmacol 1999;22:312–317
3. Schmitt U, Hiemke C. Effects of GABA-transporter (GAT) inhibitors on rat behaviour in open-field and elevated plus-maze. Behav Pharmacol 1999;10:131–137
4. Hamilton M. The assessment of anxiety states by rating. Br J Med Psychol 1959;32:50–55
5. Bandelow B. Assessing the efficacy of treatments for panic disorder and agoraphobia, 2: the Panic and Agoraphobia Scale. Int Clin Psychopharmacol 1995;10:73–81
6. Lancel M, Faulhaber J, Deisz RA. Effect of the GABA uptake inhibitor tiagabine on sleep and EEG power spectra in the rat. Br J Pharmacol 1998;123:1471–1477
7. Faulhaber J, Steiger A, Lancel M. The $GABA_A$ agonist THIP produces slow wave sleep and reduces spindling activity in NREM sleep in humans. Psychopharmacology (Berl) 1997;130:285–291

Peter Zwanzger, M.D.
Thomas C. Baghai, M.D.
Cornelius Schüle, M.D.
Christo Minov, M.D.
Frank Padberg, M.D.
Hans-Jürgen Möller, M.D.
Rainer Rupprecht, M.D.
Ludwig-Maximilians-University of Munich
Munich, Germany

Switching From Benzodiazepines to Buspirone Using a Tapered Overlap Method in Generalized Anxiety Disorder

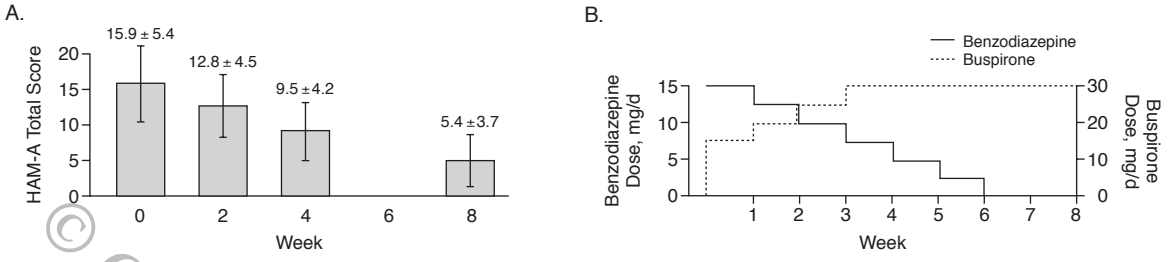
Sir: In a recent *Journal* article (February 2000), DeMartinis et al.[1] elegantly demonstrated the difficulties of switching from a benzodiazepine (BZD) to buspirone in generalized anxiety disorder (GAD). Their findings, based on a large data set of double-blind, randomized trials (N = 735), have confirmed and extended their earlier observations[2] that prior or current use of BZDs could result in reduced efficacy and tolerability of buspirone treatment in GAD. Following the earlier suggestions by Schweizer and Rickels[3] to pretreat patients with buspirone prior to undertaking a gradual taper of the BZD, my colleagues and I have demonstrated a smooth and successful transition from BZD to buspirone treatment in a recent open trial in a primary care setting.[4] This type of combination treatment, tapered overlap, is usually not allowed in controlled trials, but it is probably a feasible solution in a natural setting, i.e., in clinical practice. Delle Chiaie and colleagues[5] have found in a double-blind, placebo-controlled study that a 2-week gradual taper of previous lorazepam treatment with a simultaneous daily dose of 15 mg of buspirone can prevent clinically significant benzodiazepine withdrawal–related symptoms. This open-label trial confirms their findings, suggesting that a slow, gradual tapering with the simultaneous use of buspirone (30 mg/day) may result in a safe switch from BZDs to buspirone.

Method. A total of 78 patients (from 10 family physicians) with DSM-IV GAD (60 women and 18 men, mean age = 52 years; range, 18–65 years) had been on BZD treatment for at least 3 months. The daily dose was 15 mg of diazepam (N = 28) or the equivalent, mostly chlordiazepoxide (N = 23) or medazepam (N = 16). The patients showed only partial response to the previous relatively modest BZD dose and required further treatment. The medication regimen and the changes in the main outcome measure—total score on the Hamilton Rating Scale for Anxiety[6] before and during the 8-week study period—are summarized in Figure 1.

Results. The combined treatment and the buspirone monotherapy were well tolerated. Only 3 patients dropped out of the study because of side effects. The majority (78%; 61/78) were pleased/very pleased with the outcome of the treatment. According to the Clinical Global Impressions-Improvement scale,[7] 71% (55/78) of the patients showed much/very much improvement by the end of the 8-week study period.

Discussion. The low dropout rate compared with the results of a few similar studies, reviewed by Schweizer and Rickels,[3]

Figure 1. Switch From Benzodiazepine to Buspirone Treatment for Patients (N = 78) With Generalized Anxiety Disorder: (A) Mean ± SD Hamilton Rating Scale for Anxiety (HAM-A) Total Scores Before and During 8 Weeks of Buspirone Treatment (last observation carried forward) and (B) Dosage Regimen[a]



[a]The symptom reduction was significant ($p < .001$) compared with the baseline (week 0) value at each timepoint; nonparametric Friedman-Kendall test.

can be explained by several factors. We used a 6-week-long, gradual, slow tapering (16.6% dose reduction per week); in the first 3 weeks of the tapering period, the dose of the simultaneously administered buspirone was increased to 30 mg/day in 3 weeks.

We agree with the suggestions of DeMartinis et al.[1] that the initiation of buspirone therapy in GAD patients on BZD treatment should be undertaken cautiously and combined with appropriate patient education. Our data, in accord with the proposals by Schweizer and Rickels,[3] suggest that using tapered overlap can be a helpful, safe alternative.

This study was supported by EGIS Pharmaceuticals, Budapest, Hungary.

References

1. DeMartinis N, Rynn M, Rickels K, et al. Prior benzodiazepine use and buspirone response in the treatment of generalized anxiety disorder. J Clin Psychiatry 2000;61:91–94
2. Schweizer E, Rickels K, Lucki I. Resistance to the anti-anxiety effect of buspirone in patients with a history of benzodiazepine use. N Engl J Med 1986;314:719–720
3. Schweizer E, Rickels K. Strategies for treatment of generalized anxiety in the primary care setting. J Clin Psychiatry 1997;58 (suppl 3):27–33
4. Arató M. Buspirone in generalized anxiety. Gyogyszereink 2000;50: 215–220
5. Delle Chiaie R, Pancheri P, Casacchia M, et al. Assessment of the efficacy of buspirone in patients affected by generalized anxiety disorder, shifting to buspirone from prior treatment with lorazepam: a placebo-controlled, double-blind study. J Clin Psychopharmacol 1995;15:12–19
6. Hamilton M. The assessment of anxiety states by rating. Br J Med Psychol 1959;32:50–55
7. Guy W. ECDEU Assessment Manual for Psychopharmacology. US Dept Health, Education, and Welfare publication (ADM) 76-338. Rockville, Md: National Institute of Mental Health; 1976:218–222

Mihaly Arató, M.D., Ph.D.
University of Calgary
Calgary, Alberta, Canada

Corrections

The affiliation and address for Paul P. Doghramji, M.D., in his article "Detection of Insomnia in Primary Care" (Supplement 10, page 18) should be Brookside Family Practice, 1555 Medical Dr., Pottstown, PA 19464.

The article "Paroxetine in the Treatment of Generalized Anxiety Disorder: Results of a Placebo-Controlled, Flexible-Dosage Trial" by Mark H. Pollack, M.D., and colleagues (May 2001 issue, pp. 350–357) was accepted on March 28, 2001.

The staff regrets these errors.